Induction and Autoinduction Properties of Rifamycin Derivatives: A Review of Animal and Human Studies

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Animal studies have demonstrated that the mouse and rabbit are far more responsive to the inductive properties of rifamycin derivatives than the rat and guinea pig. The rat hepatic cytochrome P450 system seems to be resistant to the action of rifampicin unless very high doses are used. Mouse hepatic microsomal mixed-function oxidase activity is markedly increased by repeated dosing with rifampicin, whereas administration of rifabutin may be ineffective. In humans, both rifampicin and rifabutin are extensively metabolized and induce their own metabolism. The induced metabolic pathways remain essentially unknown. Under autoinduction conditions, the elimination half-life of rifampicin decreases, whereas that of rifabutin is not altered. Although the effects of repeated administration of rifampicin and rifabutin on the various forms of cytochrome P450 in humans have not been extensively examined, there is convincing evidence that the P4503A subfamily is induced by either drug, whereas the P4501A subfamily and P4502D6 do not appear to be affected by rifampicin. Limited reliable information is available concerning the induction of human glucuronyltransferase activities by rifampicin and rifabutin which, however, do not seem to influence zidovudine glucuronide formation in healthy subjects. — Environ Health Perspect 102(Suppl 9):101–105 (1994)

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Introduction

Rifampicin (RIM) and rifabutin (RIB), whose chemical structures are given in Figure 1, are two rifamycin derivatives used for the treatment of pulmonary tuberculosis. In addition to being more potent than RIM against *M. tuberculosis*, RIB proved to be beneficial to patients with chronic drug-resistant pulmonary tuberculosis unresponsive to previous treatments, including those containing RIM.

This review deals mainly with the induction and autoinduction properties of RIM and RIB in humans. However, data obtained in laboratory animals will also be discussed, as it appears that important species differences have been observed concerning the induction properties of RIM.

Induction Properties of Rifampicin and Rifabutin in Animals

Pessayre and Mazel (*1*) found that repeated administration of RIM to male ICR-Swiss mice (50 mg/kg, ip, daily for 6 days) affected the components of the hepatic mixed-function oxidase system as well as enzymatic activity. Liver weight, cytochrome P450, total heme, and NADPH-cytochrome c reductase were all significantly increased, as was the metabolism of ethylmorphine, zoxazolamine, benzpyrene, and 17β-estradiol. In contrast to the above substrates, aniline hydroxylation and the glucuronylconjugation of *p*-nitrophenol were essentially unaffected. In male Sprague-Dawley rats given RIM at the dose of 50 mg/kg, ip, twice daily for 6 days, no significant effects were observed on liver microsomal activity against five different substrates. Hexobarbital sleeping time, hepatic microsomal protein, cytochrome P450, and liver weight were also unaffected. Thus, there is a sharp species difference with respect to induction of hepatic microsomal mixed-function oxidase activity by RIM. The absence of RIM induction of drug-metabolizing enzymes in rats had been previously reported (*2*).

Species differences in RIM induction have been seen by multiple investigators. Barone et al. (*3*) found that pentobarbital and hexobarbital metabolism and hepatic cytochrome P450 levels were increased in mice treated with RIM, whereas no changes were observed in rats and guinea pigs. However, an RIM-induced rise in hepatic smooth endoplasmic reticulum was reported in guinea pigs (*4*). The inductive properties of RIM in mice were further characterized in comparison with known inducers by Heubel and Netter (*5*) and Tredger et al. (*6*), using male NMRI and C57Bl6 mice, respectively. The latter strain was also responsive to polycyclic hydrocarbon induction (*7*). Although some apparent contradictions were observed among the different studies, RIM behaved as an atypical inducer in mice, and may preferentially induce the hepatic mixed-function oxidation of large polycyclic cytochrome P450 substrates.

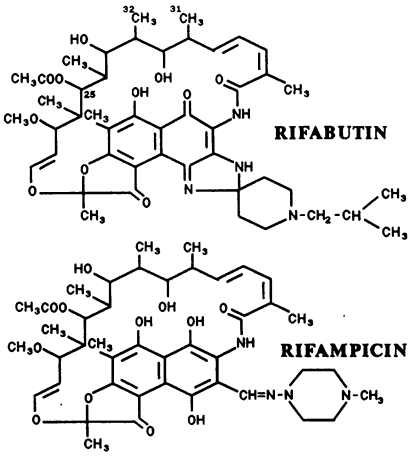

Figure 1. Chemical structures of rifampicin and rifabutin.

In contrast to mouse, rat is far less sensitive to RIM induction. In a recent work (*8*) where Wistar rats were treated orally with a 200 mg/kg dose of RIM for 7 days, no induction of the hepatic cytochrome P450 system could be

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demonstrated. In the New Zealand rabbit, Daujat et al. (*9*) reported a strong induction of hepatic cytochrome P4503A subfamily after ip administration of 50 mg/kg/day RIM for 4 days. In the same study, induction of hepatic cytochrome P4503A was also found in Wistar rats given the much higher dose of 300 to 600 mg/kg/day RIM, mixed into the ground chow, for 3 weeks. Specifically the average erythromycin-demethylase activities in liver microsomes of these rats were 0.92, 3.83, 2.11, and 4.02 nmol/mg/min in untreated and RIM-treated female and male rats, respectively.

Concerning the inductive properties of RIB, no changes in cytochrome P450 concentrations or NADPH-cytochrome c reductase, aminopyrine demethylase and aniline hydroxylase activities in liver microsomes were found in a limited study (*10*), in which RIB was given orally to female and male mice at doses up to 64 mg/kg/day for 5 to 10 days. In the same study when RIM was administered to mice according to the same schedule, the inducing properties of RIM were confirmed.

Induction Properties of Rifampicin and Rifabutin in Humans

Perucca et al. (*11*) compared the inductive properties of RIM and RIB in eight normal subjects according to a randomized crossover design. Each subject received two separate 7-day oral treatments with either RIM or RIB at the effective dosage used in clinical trials for the treatment of tuberculosis, 600 mg and 300 mg, respectively. There was a wash-out interval of at least 8 weeks between treatments. Antipyrine was administered iv 2 days before each treatment and blood samples were collected for the determination of plasma antipyrine pharmacokinetics. Blood was also collected for the measurement of plasma γ-glutamyltranspeptidase (GGT) activity. Urine was collected for the measurement of antipyrine metabolites, 6-β-hydroxycortisol (6-β-OHC) and 17-hydroxycorticosteroids (17-OHCS). The same blood and urine sampling schedule was repeated on day 7 of each treatment period, when a second antipyrine injection was given.

Antipyrine is oxidized to three main metabolites in humans: norantipyrine (NORA), 4-hydroxyantipyrine (OHA), and 3-hydroxymethylantipyrine (HMA) (*12*). There is evidence that the different metabolites are products of different forms of cytochrome P450. While cytochrome P4502D6, the isozyme of cytochrome P450 responsible for the debrisoquine/sparteine polymorphism, does not appear to be involved (*13,14*), controversial opinions have been expressed as to the participation of the cytochrome P4503A subfamily in the metabolism of antipyrine (*15,16*).

Administration of RIM was associated with a 40% shortening of the antipyrine half-life and a marked increase in antipyrine clearance. RIB caused a 25% decrease in antipyrine half-life and a moderate increase in antipyrine clearance, and these changes were significantly lower than those caused by RIM. After RIM the rate of formation, expressed as clearance for production (*17*), of NORA, OHA and HMA increased by 177, 91, and 70%, respectively, whereas only the clearance for production of NORA was significantly increased by 53% after RIB. These results are in reasonable agreement with those reported in previous studies (*17,18*), in which RIM was shown to preferentially stimulate the formation of NORA in humans. This is in contrast to phenytoin and carbamazepine which mostly enhance the formation of OHA, to a lesser degree that of HMA, and have no effect on the NORA pathway (*19*). Plasma GGT activity showed a slight but statistically significant increase after RIM and remained unchanged after RIB, thereby confirming the poor value of this enzyme as an index of the mixed-function oxidase activity (*20–22*). Urinary 6-β-OHC increased after both drugs, but the changes were significantly more marked after RIM. On average, the rise in 6-β-OHC/17-OHCS ratio over baseline (*23*) was 320% after RIM as compared to 64% after RIB.

6-β-OHC is a minor metabolite of cortisol formed primarily in the endoplasmic reticulum of hepatocytes by the mixed function oxidases and excreted unconjugated in urine. Ged et al. (*24*) have recently shown that the daily administration of a 600 mg dose of RIM for 4 days to patients results in the increase in urinary 6-β-OHC with a parallel increase in activity of liver microsomal cortisol 6β-hydroxylase and erythromycin *N*-demethylase, a marker of the cytochrome P4503A subfamily, whereas no concomitant increase is observed for the microsomal ethoxyresorufin *O*-deethylase, a marker of the cytochrome P4501A subfamily. These results indicate that the cytochrome P4503A subfamily is predominantly involved in cortisol 6β-hydroxylation, so that the increase in urinary excretion of 6-β-OHC can be considered as a marker of human hepatic cytochrome P4503A induction. In humans, cytochrome P4503A is involved in the metabolism of a large number of drugs, among which is ethynylestradiol, a constituent of oral contraceptives (*25*). Thus, the older works of Bolt et al. (*26*) and Back et al. (*27*) showing a rise in estradiol and ethynylestradiol hydroxylation in hepatic microsomal preparations from RIM-treated patients and a significant alteration of the plasma pharmacokinetics of ethynylestradiol in women treated with RIM, should be considered as a further evidence that RIM substantially induces the cytochrome P4503A subfamily.

RIB has been found to be effective for the treatment of *mycobacterium avium* complex (MAC) infection in patients with AIDS (*28,29*), and zidovudine (AZT) is currently used to treat these patients. Metabolism of AZT is species-dependent. In man, AZT is mainly excreted in urine as 5'-*O*-glucuronide (GAZT). Following oral administration, the mean urinary recovery of AZT and GAZT was 14 and 75% of the dose, respectively (*30*). In contrast, rats orally dosed with AZT excreted 78% of the dose as unchanged drug and less than 2% as GAZT in urine, while 20% of the dose was recovered as 3'-aminoderivative in feces (*31,32*). Since AZT is mainly inactivated by glucuronyl conjugation in humans, a study was carried out in healthy volunteers to examine whether, and eventually to what extent, RIB and RIM might influence the glucuronyl conjugation of AZT. The inductive effect of RIM on glucuronidation of drugs and endobiotics in humans remains a controversial question. Thus, although RIM has been shown to induce the formation of paracetamol glucuronide in humans (*33,34*), as isoniazid was given concomitantly and isoniazid was found to induce uridine diphosphate glucuronyltransferase (UDP-GT) activity in hamsters (*35*), this effect might be, at least partly, due to isoniazid. Bilirubin undergoes glucuronidation prior to excretion in the bile. There are data suggesting that RIM might enhance the hepatic clearance of bilirubin (*36–38*). However, in a study conducted in subjects given RIM for 30 days, bilirubin GT activity was reported to be insensitive to the treatment (*39*). In contrast, the paranitrophenol GT activity was significantly increased in these subjects. In humans, compound glucuronidation involves a number of isozymes, which probably differ in terms of substrate specificity and regulation (*40*). This is why it was important to examine whether the

activity of the GTs involved in the metabolism of AZT is modified by the administration of rifamycin derivatives.

Two groups of ten healthy volunteers were treated with AZT (200 mg, po) on day 1, then with RIB (300 mg/day, po) or with RIM (600 mg/day) from day 2 to day 11. On day 12 they received a further dose of 200 mg AZT. Plasma levels of AZT and of GAZT were assayed by HPLC. Urinary excretion could be studied only for AZT (*41*). C_{max} and $AUC_{0-\infty}$ of AZT were significantly decreased by either treatment, whereas no changes were observed in half-life. Eleven percent of the dose was recovered in urine as AZT and this value was not modified by RIB, but was significantly decreased by RIM. No significant difference was observed for the plasma C_{max}, $AUC_{0-\infty}$ and half-life values of GAZT between pre- and postdosing with RIB or RIM. Thus, RIB and RIM have been found to influence the metabolism of AZT in healthy subjects; this effect appears to be more marked for RIM than for RIB, at least under the experimental conditions of this study. The changes in the metabolism of AZT caused by the two rifamycin derivatives remain to be determined. It does not seem, however, that the phenobarbital-induced UDP-GT form (*42*) responsible for the formation of GAZT is involved. Although the recovery of AZT and GAZT in human urine accounts for about 90% of the dose, it may be that a minor oxidative pathway is induced by the antibiotics, or that the two rifamycin derivatives induce intracellular kinases converting AZT to nucleotide forms (*43*).

Autoinduction Properties of Rifabutin and Rifampicin in Humans

RIB is metabolized in humans to more than 20 compounds (*44*). Besides the unchanged drug, 25-*O*-deacetyl RIB has been identified in human urine together with four metabolites produced by oxidative pathways: 31-OH-RIB, 32-OH-RIB, 32-OH-25-*O*-deacetyl-RIB and 25-*O*-deacetyl-RIB-piperidine-*N*-oxide. Preliminary data on β-glucuronidase hydrolysis of human urine after RIB administration showed the presence of small amounts of conjugated RIB (P Duchene, unpublished observation).

Autoinduction of RIB metabolism was studied in seven healthy male volunteers who received 450 mg RIB orally on day 1. Then, from day 6 onwards, the same daily dose was given for 10 days (*45*). Plasma kinetics of RIB, 25-*O*-deacetyl-RIB and 31-OH-RIB were measured after the single and the last dose using HPLC with UV detection. Monitoring of plasma levels during the repeated treatment was also carried out 24 hr after the third, fifth, seventh and ninth dose. Urinary excretion of unchanged RIB, 25-O-deacetyl-RIB and 31-OH-RIB was also determined after the single and the last dose of the repeated treatment. The plasma pharmacokinetic parameters of RIB after the single and the tenth dose of the repeated treatment were calculated by model independent analysis. The experimental AUC_{0-24hr} after the tenth dose, i.e., at steady state, was significantly lower than the experimental $AUC_{0-\infty}$ after the single dose. In contrast, the difference in the half-life of elimination did not attain significance. The experimental and theoretical plasma levels of unchanged RIB 24 hr after the single dose, and 24 hr after the third, fifth, seventh, ninth and tenth dose of the repeated treatment were compared and, from the fifth dose on, the experimental values were significantly lower than the theoretical ones. These results clearly demonstrate that RIB induces its own metabolism. The plasma levels of the 25-*O*-deacetyl-RIB decreased, whereas those of 31-OH-RIB after repeated administration increased. The absence of a decrease in the half-life of elimination after RIB autoinduction could be expected for a drug with a high hepatic extraction ratio, as already suggested for metoprolol and propranolol, whose elimination half-lives were unchanged after repeated administration of RIM (*46,47*). It may also be that the metabolism of RIB is not only hepatic but also extrahepatic, with the gut participating extensively in its metabolism. Induction of gut enzymes by RIB may occur, as suggested for RIM; this might explain why the AUC was significantly reduced after repeated administration of RIB without a significant decrease in half-life of elimination.

Autoinduction of RIM metabolism in humans was studied by Acocella et al. (*48*) and more recently by Loos et al. (*49*). In the study by Acocella et al., three dose levels, each in six healthy subjects, were investigated: 900 mg and 600 mg once daily and 300 mg administered at 12-hr intervals. On days 1, 4, 6, and 14 of treatment, serum kinetics of RIM were carried out using a microbiological, nonspecific method. The pharmacokinetic parameters after the single and the repeated doses were calculated by model independent analysis. The half-life value of RIM was much shorter than that of RIB—between 2.6 and 5.1 hr following single doses. As observed for RIB, the AUC and C_{min} values of RIM decreased after repeated administration, whereas, in contrast to RIB, the half-life of elimination also decreased. The authors suggested that these changes occur mainly during the first 6 days of treatment. Deacetylation to form deacetyl-RIM and hydrolysis to afford formyl-RIM occur during RIM metabolism (*50*), and urine deacetyl-RIM decreased after repeated administration of RIM (*49*). The possible occurrence of very small amounts of the *N*-demethylderivative (*51*) and of RIM-quinone (*26,52*) in human urine clearly needs further supportive evidence, as also the possible induction (*50*) of RIM-glucuronidation (*53*).

Conclusions

The two rifamycin derivatives, RIM and RIB, induce several cytochrome P450 enzymes in humans, including those belonging to the cytochrome P4503A subfamily. The lack of induction of the cytochrome P4501A subfamily and of cytochrome P4502D6 (*14*) observed with RIM has still to be demonstrated for RIB. Both RIM and RIB induce their own metabolism. In the case of RIB, there is evidence that hydroxylation of the ansa chain is among the metabolic pathways induced, whereas in the case of RIM the induced pathways have not been identified. Following RIM autoinduction, both the area under the plasma concentration-time curve and the half-life of elimination are reduced, whereas in the case of RIB autoinduction, the half-life of elimination is not altered significantly. Although RIM may induce the glucuronidation of some xenobiotics in humans, neither RIM nor RIB appear to induce the glucuronyltransferase(s) responsible for the metabolism of AZT.

REFERENCES

1. Pessayre D, Mazel P. Induction and inhibition of hepatic drug metabolizing enzymes by rifampin. Biochem Pharmacol 25:943–949 (1976).
2. Remmer H, Schoene B, Fleischmann RA. Induction of the unspecific microsomal hydroxylase in the human liver. Drug Metab Disp 1:224–230 (1973).
3. Barone D, Beretta E, Tenconi LT. Rifampicin and liver drug-metabolizing systems: studies in guinea-pigs, rats and mice. Acta Vitaminol Enzymol 26:124–125 (1972).
4. Jezequel AM, Orlandi F, Tenconi LT. Changes of the smooth endoplasmic reticulum induced by rifampicin in human and guinea-pig hepatocytes. Gut 12:984–987 (1971).
5. Heubel F, Netter KJ. Atypical inductive properties of rifampicin. Biochem Pharmacol 28:3373–3378 (1979).
6. Tredger JM, Smith HM, Powell-Jackson PR, Davis M, Williams R. Effect of rifampicin on the mouse hepatic mixed-function oxidase system. Biochem Pharmacol 30:1043–1051 (1981).
7. Boobis AR, Nebert DW, Felton JS. Comparison of β-naphthoflavone and 3-methylcholanthrene as inducers of hepatic cytochrome(s) P-448 and aryl hydrocarbon (benzo[a]pyrene) hydroxylase activity. Mol Pharmacol 13:259–268 (1977).
8. Adachi Y, Nanno T, Yamashita M, Ueshima S, Yamamoto T. Induction of rat liver bilirubin-conjugating enzymes and glutathione S-transferase by rifampicin. Gastroenterol Jap 20:104–110 (1985).
9. Daujat M, Pichard L, Fabre I, Pineau T, Fabre G, Bonfils C, Maurel P. Induction protocols for cytochromes P450IIIA *in vivo* and in primary cultures of animal and human hepatocytes. In: Methods in Enzymology, vol 206 (Abelson JN, Simon MI, Colowick SP, Kaplan NO, Waterman MR, Johnson EF, eds). New York:Academic Press, 1991;345–353.
10. Carpentieri M, Moretti A. Lack of interaction on hepatic drug metabolizing systems by compound LM 427: comparison with rifampicin. In: Proceedings of the 6th International Symposium on Microsomes and Drug Oxidations, 5–10 August 1984, Brighton. Book of Abstracts, 53.
11. Perucca E, Grimaldi R, Frigo GM, Sardi A, Mönig H, Ohnhaus EE. Comparative effects of rifabutin and rifampicin on hepatic microsomal enzyme activity in normal subjects. Eur J Clin Pharmacol 34:595–599 (1988).
12. Danhof M, Verbeek RMA, van Boxtel CJ, Boeijinga JK, Breimer DD. Differential effects of enzyme induction on antipyrine metabolite formation. Br J Clin Pharmacol 13:379–386 (1982).
13. Balant LP, Balnt-Gorgia AE, Gex-Fabry M, Eichelbaum M. Genetic polymorphisms in human drug metabolism. In: New Trends in Pharmacokinetics (Rescigno A, Thakur AK, eds). New York:Plenum Press, 1991;391–410.
14. Eichelbaum M, Mineshita S, Ohnhaus EE, Zekorn C. The influence of enzyme induction on polymorphic sparteine oxidation. Br J Clin Pharmacol 22:49–53 (1986).
15. Pazzucconi F, Malavasi B, Galli G, Franceschini G, Calabresi L, Sirtori CR. Inhibition of antipyrine metabolism by low-dose contraceptives with gestodene and desogestrel. Clin Pharmacol Ther 49:278–284 (1991).
16. Back DJ, Maggs JL, Purba HS, Newby S, Park BK. 2-Hydroxylation of ethinylestradiol in relation to the oxidation of sparteine and antipyrine. Br J Clin Pharmacol 18:603–607 (1984).
17. Teunissen MWE, Bakker W, Meerburg-van der Torren JE, Breimer DD. Influence of rifampicin treatment on antipyrine clearance and metabolite formation in patients with tuberculosis. Br J Clin Pharmacol 18:701–706 (1984).
18. Toverud E-L, Boobis AR, Brodie MJ, Murray S, Bennett PN, Whitmarsh V, Davies DS. Differential induction of antipyrine metabolism by rifampicin. Eur J Clin Pharmacol 21:155–160 (1981).
19. Shaw PN, Houston JB, Rowland M, Hopkins K, Thiercelin JF, Morselli PL. Antipyrine metabolite kinetics in healthy volunteers during multiple dosing of phenytoin and carbamazepine. Br J Clin Pharmacol 20:611–618 (1985).
20. Park BK, Breckenridge AM. Clinical implications of enzyme induction and enzyme inhibition. Clin Pharmacokinet 6:1–24 (1981).
21. Perucca E. Clinical consequences of microsomal enzyme-induction by antiepileptic drugs. Pharmacol Ther (C) 2:285–314 (1978).
22. Barry M, Feely J. Enzyme induction and inhibition. Pharmacol Ther 48:71–94 (1990).
23. Ohnhaus EE, Park BK. Measurements of urinary 6-β-hydroxycortisol excretion as an *in vivo* parameter in the clinical assessment of the microsomal enzyme-inducing capacity of antipyrine, phenobarbitone and rifampicin. Eur J Clin Pharmacol 15:139–145 (1979).
24. Ged C, Rouillon JM, Pichard L, Combalbert J, Bresson N, Bories P, Michel H, Beaune P, Maurel P. The increase in urinary excretion of 6β-hydroxycortisol as a marker of human hepatic cytochrome P450IIIA induction. Br J Clin Pharmacol 28:373–387 (1989).
25. Guengerich FP. Oxidation of 17α-ethynylestradiol by human liver cytochrome P450. Mol Pharmacol 33:500–508 (1988).
26. Bolt HM, Kappus H, Bolt M. Effect of rifampicin treatment on the metabolism of oestradiol and 17α-ethinyloestradiol by human liver microsomes. Eur J Clin Pharmacol 8:301–307 (1975).
27. Back DJ, Breckenridge AM, Crawford FE, Hall JM, MacIver M, L'E Orme M, Rowe PH, Smith E, Watts MJ. The effect of rifampicin on the pharmacokinetics of ethynylestradiol in women. Contraception 21:135–143 (1980).
28. Lippe M, Drennan D, Bianchine J, Schoenfelder J, Wynne B. Rifabutin therapy for mycobacterium avium complex (MAC) disease in AIDS patients. In: Proceedings of the VII International Conference on AIDS. Satellite Symposium: Therapeutic Approach to Mycobacterial Infections in AIDS, 18 June 1991, Florence. Book of Abstracts, 25–28.
29. Narang P, Nightingale S, Manzone C, Colborn D, Wynne B, Li R, Watson D, Barris N, Blaschke T, Bianchine J. Does rifabutin (RIF) affect zidovudine (ZDV) disposition in HIV positive patients? In: Proceedings of the VIII International Conference on AIDS/III STD World Congress, 19–24 July 1992, Amsterdam. Book of Abstracts, B239.
30. Blum MR, Liao SHT, Good SS, De Miranda P. Pharmacokinetics and bioavailability of zidovudine in humans. Am J Med 85 (Suppl 2A):189–194 (1988).
31. De Miranda P, Burnette TC, Good SS. Disposition and pharmacokinetics of the antiviral drug 3'-azido-3'-deoxythymidine (RETROVIR) in monkeys and rats. In: Proceedings of the 27th International Conference on Antimicrobial Agents and Chemotherapy. 4–7 October 1987, New York. Book of Abstracts, 162.
32. Resetar A, Spector T. Glucuronidation of 3'-azido-3;'-deoxythymidine: human and rat enzyme specificity. Biochem Pharmacol 38:1389–1393 (1989).
33. Prescott LF, Critchley JAJH, Balali-Mood M, Pentland B. Effects of microsomal enzyme induction on paracetamol metabolism in man. Br J Clin Pharmacol 12:149–153 (1981).
34. Bock KW, Wiltfang J, Blume R, Ullrich D, Bircher, J. Paracetamol as a test drug to determine glucuronide formation in man: effects of inducers and of smoking. Eur J Clin Pharmacol 31:677–683 (1987).
35. Constantopoulos A, Loupa H, Krikos X. Augmentation of hepatic uridine-diphosphate glucuronyl transferase activity by antituberculous drugs in hamsters *in vivo*. Cytobios 52:185–191 (1987).
36. Hoensch HP, Balzer K, Dylewizc P, Kirch W, Goebell H,

Ohnhaus EE. Effect of rifampicin treatment on hepatic drug metabolism and serum bile acids in patients with primary biliary cirrhosis. Eur J Clin Pharmacol 28:475–477 (1985).
37. McColl KEL, Thompson GG, El Omar E, Moore MR, Goldberg A. Porphyrin metabolism haem biosynthesis in Gilbert's syndrome. Gut 28:125–130 (1987).
38. McColl KEL, Thompson GG, El Omar E, Moore MR, Park BK, Brodie MJ. Effect of rifampicin on haem and bilirubin metabolism in man. Br J Clin Pharmacol 23:553–559 (1987).
39. Hakim, J, Feldmann G, Boivin P, Troube H, Boucherot J, Penaud J, Guibout P, Kreis B. Etude comparative des activitées bilirubine et paranitrophénol glucuronyl transférasiques hépatiques. III. Effet de la rifampicine seule ou associée à la streptomycine et à l'isoniazide chez l'homme. Pathol Biol 21:255–263 (1973).
40. Miners JO, Mackenzie PI. Drug glucuronidation in humans. Pharmacol Ther 51:347–369 (1991).
41. Strolin Benedetti M, Duchene P, Olliaro P. Investigation on a possible induction of AZT glucuronidation by rifabutin and rifampicin in humans. In: Proceedings of the Third International ISSX Meeting, 24–28 June 1991, Amsterdam. Book of Abstracts, 295.
42. Haumont M, Magdalou J, Lafraurie C, Ziegler J-M, Siest G, Colin J-N. Phenobarbital inducible UDP-glucuronosyltransferase is responsible for glucuronidation of 3'-azido-3'-deoxythymidine: characterization of the enzyme in human and rat liver microsomes. Arch Biochem Biophys 281:264–270 (1990).
43. Furman PA, Fyte JA, St. Clair MH, Weinhold K, Rideout JL, Freeman GA, Lehrman SN, Bolognesi DP, Broder S, Mitsuya H, Barry DW. Phosphorylation of 3'-azido-3'-deoxythymidine and selective interaction of the 5'-triphosphate with human immunodeficiency virus reverse transcriptase. Proc Natl Acad Sci USA 83:8333–8337 (1986).
44. Cocchiara G, Strolin Benedetti M, Vicario GP, Ballabio M, Gioia B, Vioglio S, Vigevani A. Urinary metabolites of rifabutin, a new antibacterial agent, in human volunteers. Xenobiotica 19:769–780 (1989).
45. Strolin Benedetti M, Efthymiopoulos C, Sassella D, Moro E, Repetto M. Autoinduction of rifabutin metabolism in man. Xenobiotica 20:1113–1119 (1990).
46. Bennett PN, John VA, Whitmarsh VB. Effect of rifampicin on metoprolol and antipyrine kinetics. Br J Clin Pharmacol 13:387–391 (1982).
47. Herman RJ, Nakamura K, Wilkinson GR, Wood AJJ. Induction of propranolol metabolism by rifampicin. Br J Clin Pharmacol 16:565–569 (1983).
48. Acocella G, Pagani V, Marchetti M, Baroni GC, Nicolis FB. Kinetic studies on rifampicin. Chemotherapy 16:356–370 (1971).
49. Loss U, Musch E, Jensen JC, Mikus G, Schwabe HK, Eichelbaum M. Pharmacokinetics of oral and intravenous rifampicin during chronic administration. Klin Wochenschr 63:1205–1211 (1985).
50. Acocella G. Clinical pharmacokinetics of rifampicin. Clin Pharmacokinet 3:108–127 (1978).
51. Winsel K, Iwainsky H, Werner E, Eule H. Trennung, Bestimmung und Pharmakokinetik von Rifampicin und seinen Biotransformationsprodukten. Pharmazie 31:95–99 (1976).
52. Sunahara S, Nakagawa H. Metabolic study and controlled clinical trials of rifampin. Chest 61:526–532 (1972).
53. Nakagawa H, Sunahara S. Rifampicin-glucuronide in human urine. In: Rifampicin (Dickinson LM, ed). Amsterdam: Excerpta Medica, 1974;90–94.